Effect of Recombinant Factor VIIa as an Adjunctive Therapy in Damage Control for Wartime Vascular Injuries: A Case Control Study

Charles J. Fox, MD, Sumeru G. Mehta, MD, E. Darrin Cox, MD, John F. Kragh, Jr., MD, Jose Salinas, PhD, and John B. Holcomb, MD

Objectives: **Military casualties with vascular injuries often present with severe acidosis and coagulopathy that can negatively influence limb salvage decisions. We previously reported the value of a damage control resuscitation (DCR) strategy that can correct physiologic shock during simultaneous vascular reconstruction. The effect of recombinant factor VIIa (rFVIIa) on the repair of injured vessels and vascular grafts when used as an adjunctive therapy during DCR is unclear in the setting of wartime vascular injuries. The primary aim of this study was to assess the effect of rFVIIa use during DCR for vascular trauma and the impact on vessel repair.**

Methods: **A retrospective two cohort case control study was performed using the Joint Theater Trauma Registry to identify patients with major vascular injury and DCR. Group 1 (n = 12) had DCR and repair of the injured vessels. Group 2 (n = 41) included early rFVIIa as an adjunctive therapy with DCR to control bleeding and perform simultaneous vascular reconstruction.**

Results: **Age, injury severity score, presenting physiology, and operative time were similar between groups. Postoperative data show that early physiologic recovery from acidosis, coagulopathy, and anemia was associated with rFVIIa and DCR. Extremity graft failures in groups 1 and 2 (follow-up range, 10–26 months) were either from early thrombosis (1 vs. 5 $p = 1$), graft dehiscence (1 vs. 2 $p = 0.55$), or infection (1 vs. 1 $p = 0.41$) and were the result of inadequate soft tissue coverage or technical factors that eventually resulted in eight (15%) amputations. All cause mortality (group 1: 0% vs. group 2: 7.3%, $p = 1$) and amputation rates (group 1: 25% vs. groups 2: 12.2%, $p = 0.36$) were similar between the two groups.**

Conclusions: **DCR using rFVIIa is effective for controlling hemorrhage and reversing coagulopathy for severe vascular injuries. Early graft failures seem unrelated to rFVIIa use in the setting of wartime vascular injuries. No differences in amputation rate or mortality were seen. Although rFVIIa may be a useful damage control adjunct during vessel repair, the overall impact of this strategy on long-term outcomes such as mortality and limb salvage remains to be determined.**

Key Words: **Vascular trauma, Damage control, Resuscitation, Coagulopathy, Factor VIIa, Wartime, Military, Combat.**

J Trauma. 2009;66:S112–S119.

Modern advances in prehospital combat casualty care have reduced mortality for patients with vascular injuries and potential for hemorrhagic death on the battlefield.[1–3] An increase in combat-related extremity wounds during recent military operations now permit the study of contemporary resuscitation practices used in preparation for reconstructing a major vascular injury.[4] The early coagulopathy of trauma is often present at admission to the emergency department (ED) underscoring the importance that the metabolic consequences of hemorrhagic shock can negatively influence limb salvage decisions if early hemostasis is not achieved.[5,6] We previously proposed a damage control resuscitation (DCR) strategy that seems to be successful for the management of acute wartime vascular injuries with effective correction of physiologic shock.[7] This employs the use of fresh whole blood (FWB), or a high ratio (<1:1.4) of plasma to packed red blood cells (PRBCs), minimal crystalloid use, and liberal replacement of platelets and cryoprecipitate. Because coagulopathy is a major factor contributing to bleeding-related mortality even after surgical control of hemorrhage, early recombinant activated coagulation factor VII has been used during this war according to specific clinical practice guidelines.[8,9]

The use of recombinant factor VIIa (rFVIIa) to treat the acquired coagulopathy of trauma seems to be a useful adjunct to existing therapy and in some settings may reduce transfu-

Submitted for publication November 20, 2008.

Accepted for publication January 16, 2009.

From the Department of Surgery (C.J.F.), Walter Reed Army Medical Center, Washington, DC; Division of Vascular Surgery (C.J.F.), Uniformed University of the Health Sciences, Bethesda, Maryland; Department of Emergency Medicine (S.G.M.), Brooke Army Medical Center, San Antonio, Texas; Department of Surgery (E.D.C.), William Beaumont Army Medical Center, El Paso, Texas; and United States Army Institute of Surgical Research (J.F.K., J.S., J.B.H.), San Antonio, Texas.

Accepted for poster presentation at the 38th Annual meeting of the Advanced Trauma Applications for Combat Casualty Care, Saint Pete Beach, Florida, August 11, 2008.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. The authors are employees of the U.S. government. This work was prepared as part of their official duties and, as such, there is no copyright to be transferred.

Address for reprints: LTC Charles J. Fox, MD, Walter Reed Army Medical Center, Vascular Surgery, Building 2, Ward 64, 6900 Georgia Avenue, NW, Washington, DC 20307; email: Charles.Fox@us.army.mil.

DOI: 10.1097/TA.0b013e31819ce240

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 APR 2009	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Effect of recombinant factor VIIa as an adjunctive therapy in damage control for wartime vascular injuries: a case control study	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Fox C. J., Mehta S. G., Cox E. D., Kragh Jr. J. F., Salinas J., Holcomb J. B.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam houston, TX 78234	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**8**	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std Z39-18

sion requirements for severely injured patients.[10] Moreover, early administration has been reported to be superior to "last ditch" use in breaking a bloody vicious cycle.[11] Since most vascular injuries in Iraq and Afghanistan have required a massive transfusion to repair a vascular injury, the selective use of rFVIIa seems to be a relevant and important damage control adjunct but this remains unclear.[12] Previous randomized civilian placebo-controlled trials in trauma have not reported an increased incidence of severe thrombotic events. In those civilian, largely blunt injured patients vascular repair was unusual. However, significant vascular injury is common in military injuries, thus it is important to understand how an agent that promotes clotting to control bleeding may impact the immediate repair of a vascular injury.[10] The objective of this case control study was to report the effect of rFVIIa on the repair of injured vessels and vascular grafts when used as an adjunctive therapy during DCR in the setting of wartime vascular injuries. Additionally, this study aims to provide insight into the impact of rFVIIa use on early physiologic recovery after immediate limb salvage procedures for traumatic combat-related vascular injuries.

MATERIALS AND METHODS

Using the Joint Theater Trauma Registry (JTTR), two cohorts of patients treated from April 2006 to August 2007 for major wartime vascular injury at a Baghdad-based US Combat Support Hospital (CSH) were created. Basic demographic, physiologic, resuscitation, and early outcomes were compared between these cohorts. Group 1 (n = 12) and group 2 (n = 41) were similar in that both consisted of patients with wartime vascular injuries resuscitated in accordance with established DCR clinical practice guidelines. However, group 2 included early rFVIIa as an adjunctive therapy with DCR to control bleeding and perform the vascular reconstruction, whereas group 1 did not.

Included were those patients who arrived at the CSH with a life threatening hemorrhage (>4 units PRBCs) from penetrating military munitions and underwent simultaneous repair of a vascular injury, usually with reversed saphenous interposition grafting. Group 1 (control) and group 2 (rFVIIa) patients received a resuscitation strategy that included FWB or PRBCs with a high plasma ratio, and minimal crystalloids as an accepted DCR strategy for severely injured military patients in hemorrhagic shock. Group 2 (rFVIIa) included the early (preoperative) intravenous (i.v.) administration of rFVIIa for patients who had at least one indication for it use based on established guidelines (Table 1). Patients receiving DCR with isolated cervical, torso, or extremity vascular injury repaired with saphenous vein grafts were included. Also, included were any arterial injuries that had thrombectomy and lateral suture or primary repair to re-establish a pulse since these repairs in addition to saphenous grafts are vulnerable to the effects of clotting agents. The study was approved by the research committee of the participating CSH and the Brooke Army Medical Center IRB.

Table 1 Institutional Indications for the Administration of Recombinant Factor VIIa for Damage Control in Vascular Trauma Patients

Laboratory Parameter	Laboratory Value
pH	≤7.2
Base deficit	≤−6
[Hb] (g/dL)	≤11
Prothrombin time	≥16
INR	≥1.5
Systolic pressure	≤90
Temp (°F)	<96
Severe head injury	Yes
Massive transfusion	Yes
FWB transfusion	Yes

Hb, hemoglobin; Temp, temperature.

Demographic data collection included patient gender, age, Injury Severity Score, mechanism of injury, and Glasgow Coma Scale. Physiologic data collection included the initial presenting vital signs (rectal temperature, blood pressure, heart rate) and physiologic parameters that included pH, base deficit, hemoglobin (g/dL), platelet count, and international normalized ratio. Operative blood product requirements to include those units received in the emergency room were documented. The amount of transfused crystalloid, PRBCs, plasma, cryoprecipitate, and platelets were monitored. The doses and timing of the administration of rFVIIa were reported (typically 90–120 μg/kg i.v.). Patients who received a massive PRBC transfusion (≥10 units), FWB, or unfractionated heparin were also documented.

After emergent vascular reconstruction, the patient was taken to the intensive care unit (ICU) and the initial vital signs were observed. The ICU admission laboratory analysis included a postoperative complete blood count, arterial blood gas sample, and coagulation studies. The differences (Δ) in vital signs and laboratory study results obtained in the ED and the ICU were used to determine the extent of early physiologic recovery.

Primary outcome measures were normalization of the initial physiologic derangements, and a successful revascularization of the pulseless extremity as defined by restoration of a palpable pulse and establishment of a normal ankle-brachial index (>0.9). Early success was determined and reflected in early graft patency, survival, and amputation rate. Operative details including location of arterial injury, associated venous injury, type and configuration of conduit used, and procedure times were reviewed. Standard paired *t* tests (continuous variables) or Fisher's exact tests (percentage ratios) were used to determine statistical significance using SPSS 14 software (Chicago, IL).

RESULTS

During the study period 53 seriously injured patients underwent repair of 93 major vascular injuries using a strategy of early DCR and immediate vascular reconstruction. The study group consisted of 15 US service members (28%),

37 Iraqi nationals (70%), and 1 (2%) foreign contractor. All but two patients were male with an age range of 10 to 66 years. The mean military injury severity score for the population studied was 27.4 ± 14.2. Baseline demographics and admission physiology (Table 2) were similar between both cohorts. Vessel injuries were from penetrating trauma and consisted of high-energy explosions or gunshot wounds. Because of the short prehospital transport time (≈30 minutes), extremity ischemic times were limited. Prehospital tourniquet use was common (39, 74%) and all but two patients with extremity vascular injury arrived with a tourniquet applied. Major soft-tissue injury frequently led to combined orthopedic (fixation, fasciotomy) and vascular procedures, performed simultaneously.

Physiologic Effect of DCR and Early rFVIIa

The overall response to resuscitation measures were reflected in early correction of presenting physiologic imbalances on conclusion of the operative procedure for limb salvage. Table 3 demonstrates a similar degree of recovery in both cohorts. A comparison of physiologic differences from ED arrival (Table 2) with ICU admission was made and reflected by the relative change in vital signs and normalization of laboratory studies. In group 2, patients who were treated with DCR using adjunctive rFVIIa (group 2) demonstrated a physiologic recovery from the initial presenting acidosis and coagulopathy. The acidosis and anemia in the control group (no rFVIIa) was also substantially improved. Both groups show that systolic and diastolic blood pressure increased concordantly, and the heart rate decreased to an acceptable rate by the time the patient reached the ICU. Correction of anemia in the study group is reflected in the differences of blood products administered (Table 4).The INR was improved significantly in the study group but worsened in the control at the time of ICU admission. Temperature was noted to decline in the study group but did not reach statistical significance.

Patients treated using rFVIIa received more total blood products (packed cells plus whole blood), more FFP, and more cryoprecipitate than patients in group 1 treated without rFVIIa. Total blood components given were increased in the study group, and 34 patients (83%) required a massive transfusion compared with 5 patients (42%) in the control. An FFP: PRBC ratio (given at 1:1.5) in the control group closely approximated a goal of 1:1 and was similar to the ratio of 1:1.2 in group

Table 2 Demographics and Averaged Physiologic Parameters on ED Arrival in Both Cohorts

Variable	All Patients	Group 1 (Control)	Group 2 (rFVIIa)	*p*
Age (yr)	26.6 ± 9.7 (49)	24 ± 10 (10)	27.5 ± 9.4 (39)	0.31
Injury of Severity Score	27.4 ± 14.2 (53)	22.2 ± 10.7 (12)	28.9 ± 14.9 (41)	0.14
Glasgow Coma Score	13.5 ± 3.0 (53)	13.5 ± 3.6 (12)	12.9 ± 3.6 (40)	0.62
Systolic blood pressure	103 ± 31 (53)	110 ± 28 (12)	101 ± 32 (41)	0.36
Diastolic blood pressure	58 ± 20.4 (53)	55 ± 15.6 (12)	59 ± 21.8 (41)	0.61
Heart rate	126 ± 27.7 (52)	133 ± 23.4 (12)	123 ± 28.7 (40)	0.31
Temperature (°F)	99 ± 1.3 (48)	99 ± 0.98 (12)	99 ± 1.4 (36)	0.94
pH	7.23 ± 0.2 (52)	7.27 ± 0.2 (12)	7.22 ± 0.2 (40)	0.40
Base deficit	9.11 ± 6.8 (53)	8.42 ± 6.4 (12)	9.32 ± 6.9 (41)	0.69
Hb (g/dL)	9.5 ± 2.4 (53)	10.0 ± 2.0 (12)	9.4 ± 2.5 (41)	0.47
Platelet count	267 ± 112 (23)	269 ± 120 (12)	264 ± 108 (11)	0.92
INR	1.45 ± 0.6 (49)	1.35 ± 0.4 (11)	1.47 ± 0.6 (39)	0.58

p values are derived from standard *t* tests. Data are mean ± SD unless otherwise specified and the n values are given in the parentheses.
ED, emergency department; Hb, hemoglobin; INR, international normalized ratio; DCR, damage control resuscitation; rFVIIa, recombinant factor VIIa.

Table 3 Physiologic Recovery After Vascular Reconstruction in 2 DCR Cohorts ± rFVIIa

Variable	Group 1 (Control) (n)	No rFVIIa Δ	*p*	Group 2 (rFVIIa) (n)	rFVIIa Δ	*p*
Systolic blood pressure	121 ± 14 (12)	11	0.15	154 ± 35 (41)	53	0.05
Diastolic blood pressure	64 ± 11 (12)	9	0.04	70 ± 19 (41)	11	0.01
Heart rate	120 ± 31 (12)	−13	0.22	107 ± 30 (41)	−16	0.02
Temperature (°F)	98.5 ± 1.1 (11)	−0.5	0.21	97.0 ± 1.0 (41)	−2	0.28
pH	7.31 ± 0.07 (10)	0.04	0.59	7.35 ± 0.11 (37)	0.13	<0.01
Base deficit	3.5 ± 4.4 (10)	4.92	0.08	0.76 ± 6.7 (37)	8.56	<0.01
Hb (g/dL)	10.1 ± 1.3 (11)	0.1	0.81	12.3 ± 8.2 (38)	2.9	0.06
Platelet count	106 ± 46.6 (11)	−163	<0.01	108 ± 46.2 (38)	−156	<0.01
INR	1.6 ± 0.61 (11)	0.25	0.56	1.2 ± 0.58 (38)	−0.25	0.04

p values are derived from standard paired *t* tests. Data are mean ± SD unless otherwise specified.
Δ, Comparison of physiologic differences from ED arrival (Table 1) to ICU admission.
Vitals signs and laboratory studies were taken immediately at ICU admission.
Hb, hemoglobin.

Table 4 Summary of Averaged Operative Transfusion Requirements Comparing DCR and DCR With rFVIIa

Blood Component	Control	rFVIIa	*p*
Total Blood Products (OR) (U)*	6.7 ± 5.2	16.7 ± 11.2	<0.001
FFP (OR) (U)	4.5 ± 3.8	13.4 ± 9.2	<0.001
Plasma: RBC ratio	1:1.5	1:1.2	0.20
Cryoprecipitate (U)	0	10 ± 10.7	<0.001
Platelets (6pk) (U)	1.8 ± 1.1	1.19 ± 0.91	0.64
OR crystalloid (L)	3.9 ± 1.7	3.7 ± 1.7	0.74
ICU crystalloid (L)	3.8 ± 2.6	2.6 ± 2.4	0.14
ICU blood products (L)*	3.0 ± 5.8	4.2 ± 6.6	0.61
Massive transfusion (≥10 units)	42%	83%	0.002

* Packed RBCs + whole blood.
FFP, fresh frozen plasma or thawed plasma; OR, operating room.

2. A matched amount crystalloid 3.9 L versus 3.7 L was administered in both groups consistent with the DCR guidelines to minimize crystalloid fluids. Most of the patients (32, 78%) in group 2 received i.v. rFVIIa early in the emergency room resuscitation with one to two additional doses (90–120 μg/kg) given intraoperatively. The remainder of the study group had the first dose administered intraoperatively (4, 10%) or during admission to the ICU (5, 12%), for ongoing coagulopathic bleeding. Heparin was not used (40, 75%) or only limited to a half dose (13, 25%) in the combined study group. The average transfusion requirements after DCR with and without adjunctive rFVIIa are summarized in Table 4.

Damage Control and Immediate Repair of Vascular Injuries

Ninety-three vascular reconstructions for limb salvage were performed using a reversed saphenous vein graft (n = 44, 47%) or less commonly prosthetic materials (4, 4%). Interposition grafts were used in the setting of adequate muscle coverage (small wound, healthy muscle) or else a tunneled bypass graft was placed around the zone of injury (large wound, devitalized tissue). Primary repairs by lateral suture, or end-to-end anastomosis was created when possible (13, 14%) although segmental loss of the vessel was frequently encountered. Therefore, patch angioplasty was used only once. Ligation was not infrequent for arterial vessels that could be easily sacrificed as a damage control maneuver (16, 17%). These were usually distal run-off vessels of the forearm or leg. One patient each with ligation of the superficial femoral, popliteal, and tibial arteries resulted in limb loss. Additionally, one patient with a pulseless leg underwent femoral thrombectomy without repair which resulted in a transtibial amputation.

Repair of concomitant venous injury (n = 22, 24%) was favored over ligation (10, 11%), when the physiologic condition of the patient permitted the additional operative time. Saphenous vein grafts (19 of 20, 95%) were preferred and a prosthetic graft was only used for one patient. Temporary shunts were placed in five patients as a damage control adjunct. Three were followed up by immediate successful saphenous grafting. One patient was returned to the ICU for additional resuscitation, and suffered limb loss secondary to shunt thrombosis. Another died of wounds before the definitive repair was made. The median operative time required for these procedures were 270 minutes and included the time needed for DCR, laparotomy, fasciotomy, fixation, and repair of the injured vessels. Orthopedic fixation was extremely rapid and accomplished by a second team during the vein harvest from the contralateral limb. When thoracotomy or laparotomy was indicated, the orthopedic team would often apply additional tourniquets, expose the wound, and apply fixation without the use of fluoroscopy. Plain radiographs were used to guide the need for pin adjustments during subsequent washouts. Fasciotomy was performed in the majority (80%) of patients with extremity vascular injury. The distribution and management of these injuries were similar between the groups and are summarized in Tables 5 and 6.

Adjunctive Factor VIIa and Outcome of Vascular Reconstruction

Damage control maneuvers were used to repair 93 major vascular injuries in 53 seriously injured patients. The 24 hour survival was 94%. Among all patients there were 11 (21%) major graft failures from early thrombosis (6), infection (2), or sudden graft rupture with secondary hemorrhage (3). These failures led to eight amputations producing an overall amputation rate of 15%. Clinical follow-up (range, 11–27 months) was available for 14 (26.4%) patients. Nine of these repairs have remained patent as determined by clinical examination, noninvasive studies, or angiography.

Forty-one patients received rFVIIa as an adjunctive therapy in the setting of damage control surgery to control coagulopathic hemorrhage during the immediate vascular reconstruction of 72 injuries. In this cohort, there were five (12.2%) early thrombotic failures compared with only one (8.3%) in the control group. Early thrombosis in the rFVIIa group (group 2) was related to one each anastomotic stricture, graft twist, redundant graft, primary repair with downstream intimal damage, and failure to identify an injury after an initially successful balloon thrombectomy. Three of these five cases underwent successful revision and two limbs were not salvaged. Additionally, there were two graft ruptures, and one graft infection in the rFVIIa group compared with one each in the control. Three (25%) and 5 (12.2%) lower amputations were performed in groups 1 and 2 (rFVIIa), respectively. Nine of the 14 (64.3%) cases followed up during this 1- to 2-year period were from the rFVIIa group. The observed differences were not statistically significant. The outcomes of each treatment group with respect to survival and complications for these vascular injuries are shown in Table 7.

DISCUSSION

This study represents the strength of the JTTR to examine the effect on the adjunctive use of rFVIIa and refine the use of DCR in the setting of repairing major wartime vascular

Table 5 Distribution and Management of 12 Patients With 21 Vascular Injuries and DCR

Location/Vascular Injury	Suture	End-End	SV Interposition	Ligation	Shunt*	Total
Upper extremity						
Axillary			1			1
Brachial						
Ulnar				1		1
Radial	1					1
Lower extremity						
Common femoral			1		1	1
Superficial femoral			4		1	4
Deep femoral				1		1
Popliteal			3	1†		4
Tibial				1‡		1
Pedal				1		1
Venous						
Femoral		1	4			5
Popliteal				1		1
Total	1	1	13	6		21

* Temporary shunt before repair SFA (1), CFA (1).
† AKA, above knee amputation; ‡ BKA, below knee amputation; suture, primary repair; end-end, end-end anastomosis; SV, saphenous vein.

Table 6 Distribution and Management of 41 Patients With 72 Vascular Injuries Using DCR and rFVIIa

Location/Vascular Injury	Suture	Patch	End-End	Prosthetic	SV Interposition	SV Bypass	Ligation	Thrombectomy	Shunt	Total
Abdomen										
Visceral							1			1
Iliac			1		1				1*	3
Hypogastric							2			2
Neck										
External Carotid							1			1
Upper Extremity										
Subclavian				3						3
Axillary					3	1				4
Brachial					1		1			2
Ulnar					1	2†	1			4
Radial							2			2
Lower Extremity										
Common femoral					2					2
Superficial femoral					6			2‡	2§	10
Deep femoral							2			2
Popliteal					4	3‖				7
Tibial					2		2			4
Venous										
Jugular							1			1
Subclavian	1									1
Axillary	1				1		2			4
Iliac	2						2			4
Profunda femoral	1						3			4
Femoral	3	1	1	1	2		1			8
Popliteal	1				2					3
Total	9	1	2	4	25	6	20	2	3	72

* Followed by SV graft.
† Brachioulnar reversed SV bypass.
‖ Popliteal-posterior tibial reversed SV bypass.
‡ BKA (1).
§ Shunt thrombosis led to AKA (1); Died of Wounds (1).
AKA, above knee amputation; BKA, below knee amputation; suture, primary repair; end-end, end-end anastomosis; SV, saphenous vein.

injuries. Successful immediate vessel repair with early physiologic recovery using these damage control concepts validate previous reports underscoring the importance of using a hemostatic resuscitation plan for patients with vascular injuries that arrive in hemorrhagic shock and have a high potential for massive transfusion. This approach represents an

Table 7 Outcomes of Each Treatment Group With Respect to Survival and Complications

Variable	All Patients (n = 53)	Group 1 (Control) (n = 12)	Group 2 (rFVIIa) (n = 41)	*p*
Early graft thrombosis	6	1	5	1
Graft infection	2	1	1	0.41
Graft rupture	3	1	2	0.55
Long-term follow-up	14	5*	9†	0.26
Amputation (%)	15	25	12.2	0.36
24 h survival (%)	94.30	100	92.7	1

rFVIIa, recombinant factor VIIa.
P values are derived from Fisher exact test.
* 3/5 grafts patent by duplex at 12 mo.
† 6/9 grafts patent 11–27 mo.

evolution in traditional damage control philosophy where previously amputation was favored over intricate and time consuming vascular reconstruction, described as "life over limb." These findings demonstrated that derangements in physiologic conditions that have classically led us to "bail out" may no longer be a contraindication to prolonged vascular reconstruction when modern DCR resuscitation principles are used. Although typical physiologic endpoints seem achievable with DCR, the consequences of using rFVIIa on a freshly repaired vessel have not been well studied and serve as the foundation of this report.

The Central Command (CENTCOM) Clinical Practice guideline described i.v. administration of 90 to 120 μg/kg rFVIIa (usually three vials, 2.4 mg $\times$3) given first in the ED, with additional doses given intraoperatively to treat acquired coagulopathy and reduce hemorrhage.[9] The use of rFVIIa for individual casualties was based on the casualty's physiologic status, anticipated transfusion requirements, overall resuscitation response, surgical plan, and individual physician preference. Injury to multiple vessel beds or an expectation for a massive transfusion was often a practical indication for rFVIIa use. A temporal relationship with systemic clotting was observed and the goal of these interventions was a normal international normalized ratio in the operating room. Crystalloid fluids were kept to an absolute minimum to avoid dilutional coagulopathy and further iatrogenic physiologic derangement.[13] For injuries to a single extremity, rFVIIa was used sparingly and reserved for cases when hemorrhage was not surgically treatable or controlled with hemostatic dressings. Heparin, often limited to a half dose, was used infrequently, and used mostly for straightforward isolated extremity injury cases. Transfusions were started early, warmed, and infused rapidly. The ratio of PRBCs to FFP or thawed AB plasma approximated 1:1 to avoid further dilutional coagulopathy of trauma.[14–17]

The importance of treating the early coagulopathy of trauma has gained interest, because new evidence has demonstrated that an acute coagulopathy may be attributable to the injury itself and should now be a priority during the initial evaluation and treatment.[5,18] Restoration of normal physiology in the operating room allows surgeons to focus on controlling surgical bleeding and performing definitive, albeit complicated, and prolonged vascular reconstruction. The number of recent combat casualties with vascular injuries that require massive transfusion offers a chance to observe the effects of contemporary hemostatic strategies in a cohort where the thrombotic consequences of this approach may be immediately obvious. The preclinical and investigational use of rFVIIa as an adjunctive therapy for control of bleeding in patients with traumatic injuries have been described previously.[19–26] Two randomized trials designed to study the effects on trauma patients have demonstrated safe, efficacious use with an even distribution and low incidence of thromboembolic events between treatment groups.[10] Further analysis of this data demonstrated in a coagulopathic subgroup that rFVIIa reduced multiorgan failure and consumed less blood products. The authors concluded from these findings that coagulopathic trauma patients seem to benefit from early adjunctive rFVIIa therapy.[27] Recent evidence in a population of military casualties requiring massive transfusion show that rFVIIa can significantly reduce transfusion requirements when administered early (before 8 units of blood transfused). Similarly, late complications were not significantly different between study groups and only one thrombotic event was reported in 61 patients.[11] However, none of the thrombotic complications described in these particular reports were related to the repair of injured blood vessels. Spinella et al.[28] in addition demonstrated that the early use of rFVIIa was associated with decreased 30-day mortality in severely injured combat casualties requiring massive transfusion and likewise was not associated with an increased risk of severe thrombotic events. Nonetheless, given the cautionary reports on the thrombotic potential of rFVIIa use, the primary aim of this study was to assess the effect of rFVIIa use during DCR for vascular trauma and the impact of that therapy on vessel repair.[29] We found that early thrombotic failures were not significantly different between treatment groups. Graft failures in the study group (rFVIIa) related to the construction of the anastomosis, graft redundancy, or intimal damage and were all attributable to the technical aspects of the revascularization. Similarly, limb salvage and early survival rates were evenly distributed and are not significantly different. We defined the use of rFVIIa by a time frame (early = used in emergency room) and not by the administration after a

certain number of units of blood transfused. Interestingly, the overall use of blood products was not diminished in the rFVIIa group and may represent a higher proportion of surgical bleeding, greater enthusiasm for staying in the OR longer, or perhaps more liberal transfusion practices when early (ED) rFVIIa is used. Despite that finding, the degree of physiologic recovery from acidosis and coagulopathy at admission to the ICU was more complete in the rFVIIa group. Although this observation may have been attributable to the increased blood products, both groups overall had demonstrated robust physiologic improvements and therefore support the findings of our previous report on the effectiveness of DCR for military vascular trauma.[30]

The small number of patients, short observation period, and retrospective design are valid limitations of this study. The sample size increases potential for drawing an erroneous conclusion, because this study is not adequately powered for strong statistically supported interpretations. On the contrary, it is rare that successful outcomes in vascular surgery can be achieved with false-negative results (graft thrombosis not detected) as early graft failures are clinically obvious, rigorously investigated, and require immediate attention. Nonetheless, precautions against type II errors are advised when attempting to detect small differences between study groups. Extended follow-up can only be assured for US casualties, with few exceptions. Additionally, although 6 months of the study represent the authors' personal experience, it is understandably difficult to maintain complete documentation of all adverse events experienced in a combat environment. Therefore, important omissions may occur when patients are not well known to the investigating team. Despite these limitations, the findings are original and may serve to reduce concerns that rFVIIa may hinder a successful revascularization.

This report also demonstrates the ability of the JTTR to evaluate and distribute important follow-up information on established clinical practice guidelines. This form of data collection and analysis using a theater wide-trauma system should serve as a model for future wartime clinical care. The additional aspects of the outcome data in this report are persuasive and point to the value of continued investigation and refining of resuscitation practices in urban trauma centers. Although definitive guidelines regarding repair of vascular injuries in the setting of severe physiologic derangements have not fully been met, there are distinct trends in this direction. We observed that early recognition and correction of shock and coagulopathy with the DCR strategy + rFVIIa will permit the additional operative time necessary for limb salvage. In groups that had equal physiologic disturbances, adjuvant rFVIIa did not cause clinically observed differences in early thrombotic graft failures supporting our plan for its selective use in DCR. We anticipate with future analysis of JTTR data and refined use of a DCR strategy, potential benefits to combat casualties with vascular injury may be identified.

CONCLUSIONS

This study represents the first to use the JTTR to provide follow-up on the repair of major wartime vascular injuries. Resuscitation goals are obtainable when rFVIIa was used as a damage control adjunct in the management of seriously wounded casualties. The cohort of patients treated with increased volume of blood products and rFVIIa demonstrated effective correction of physiologic shock and control of coagulopathic bleeding in concert with definitive vascular reconstruction. Early thrombotic graft failures seem to be the result of technical issues unrelated to withholding heparin or use of rFVIIa as an adjunctive therapy. Early recognition and correction of a traumatic coagulopathy should be encouraged for treating vascular injuries, because breaking the "bloody vicious cycle" may afford the best chances of a successful revascularization. The overall impact of this vascular damage control strategy on long-term outcomes such as limb salvage and mortality remains to be determined although results from this study are encouraging.

REFERENCES

1. Holcomb JB, McMullin NR, Pearse L, et al. Causes of death in US Special Operations Forces in the Global War on Terrorism 2001–2004. *Ann Surg.* 2007;245:986–991.
2. Fox CJ, Starnes BW. Vascular surgery on the modern battlefield. *Surg Clin North Am.* 2007;87:1193–211, xi.
3. Kragh JF Jr, Walters TJ, Baer DG, et al. Practical use of emergency tourniquets to stop bleeding in major limb trauma. *J Trauma.* 2008; 64:S38–S49.
4. Rasmussen TE, Clouse WD, Jenkins DH, et al. Echelons of care and the management of wartime vascular injury: a report from the 332nd EMDG/Air Force Theater Hospital, Balad Air Base, Iraq. *Perspect Vasc Surg Endovasc Ther.* 2006;18:91–99.
5. Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. *J Trauma.* 2003;54:1127–1130.
6. MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. *J Trauma.* 2003;55:39–44.
7. Fox CJ, Gillespie DL, Cox ED, et al. Damage control resuscitation for vascular surgery in a combat support hospital. *J Trauma.* 2008;65:1–9.
8. Cosgriff N, Moore EE, Sauaia A, et al. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. *J Trauma.* 1997;42:857–861.
9. CENTCOM CPG. Recombinant Factor VIIa [database on the Internet]: US Department of Defense. Available at: https://jpta.fhp.osd.mil. Accessed 2007.
10. Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma.* 2005;59:8–15.
11. Perkins JG, Schreiber MA, Wade CE, et al. Early versus late recombinant factor VIIa in combat trauma patients requiring massive transfusion. *J Trauma.* 2007;62:1095–1101.
12. Beekley AC. Damage control resuscitation: a sensible approach to the exsanguinating surgical patient. *Crit Care Med.* 2008;36:S267–S274.
13. Alam HB, Rhee P. New developments in fluid resuscitation. *Surg Clin North Am.* 2007;87:55–72, vi.
14. Borgman MA, Spinella PC, Perkins J, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma.* 2007;63:805–813.

15. Hess JR, Holcomb JB, Hoyt DB. Damage control resuscitation: the need for specific blood products to treat the coagulopathy of trauma. *Transfusion.* 2006;46:685–686.
16. Gonzalez EA, Moore FA, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion 1. *J Trauma.* 2007;62:112–119.
17. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma 1. *J Trauma.* 2007;62:307–310.
18. Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: its pathophysiology and treatment in the injured patient. *World J Surg.* 2007;31:1055–1065.
19. Holcomb JB. Use of recombinant activated factor VII to treat the acquired coagulopathy of trauma. *J Trauma.* 2005;58:1298–1303.
20. Holcomb JB, Hoots K, Moore FA. Treatment of an acquired coagulopathy with recombinant activated factor VII in a damage-control patient. *Mil Med.* 2005;170:287–290.
21. Holcomb JB. Methods for improved hemorrhage control. *Crit Care.* 2004;8 (Suppl 2):S57–S60.
22. Klemcke HG, Delgado A, Holcomb JB, et al. Effect of recombinant FVIIa in hypothermic, coagulopathic pigs with liver injuries. *J Trauma.* 2005;59:155–161.
23. McMullin NR, Kauvar DS, Currier HM, et al. The clinical and laboratory response to recombinant factor VIIA in trauma and surgical patients with acquired coagulopathy. *Curr Surg.* 2006;63:246–251.
24. Mohr AM, Holcomb JB, Dutton RP, Duranteau J. Recombinant activated factor VIIa and hemostasis in critical care: a focus on trauma. *Crit Care.* 2005;9 (Suppl 5):S37–S42.
25. Schreiber MA, Holcomb JB, Rojkjaer R. Preclinical trauma studies of recombinant factor VIIa. *Crit Care.* 2005;9 (Suppl 5):S25–S28.
26. White CE, Schrank AE, Baskin TW, et al. Effects of recombinant activated factor VII in traumatic nonsurgical intracranial hemorrhage. *Curr Surg.* 2006;63:310–317.
27. Rizoli SB, Boffard KD, Riou B, et al. Recombinant activated factor VII as an adjunctive therapy for bleeding control in severe trauma patients with coagulopathy: subgroup analysis from two randomized trials. *Crit Care.* 2006;10:R178.
28. Spinella PC, Perkins JG, McLaughlin DF, et al. The effect of recombinant activated factor VII on mortality in combat-related casualties with severe trauma and massive transfusion. *J Trauma.* 2008;64:286–293.
29. Mazer CD, Leong-Poi H, Mahoney J, et al. Vascular injury and thrombotic potential: a note of caution about recombinant factor VIIa. *Semin Cardiothorac Vasc Anesth.* 2007;11:261–264.
30. Fox CJ, Gillespie DL, Cox ED, et al. The effectiveness of a damage control resuscitation strategy for vascular injury in a combat support hospital: results of a case control study. *J Trauma.* 2008;64:S99–106.